

Medical Services

Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances

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Department of the Army
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SUMMARY of CHANGE

AR 40-7

Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances

This revision includes new guidance on--

- o The postmarketing surveillance of Food and Drug Administration approved New Drug Applications that are sponsored by The Surgeon General (para 2-6).
- o The redesignation of the Army Investigational Drug Review Board as the Human Subjects Research Review Board (para 2-6).
- o The procedures for processing of non-DA-sponsored Investigational New Drug (IND) applications and Investigational Device Exemptions (IDEs) (para 3-3).
- o The procedures for processing investigator-sponsored IND applications and IDEs (para 3-4).
- o The use of investigational devices (chaps 3 and 4, apps B and D).
- o The application for use of Schedule I controlled substances in the clinical and the non-clinical setting (paras 4-5 and 4-6).
- o The use of Group C cancer chemotherapy investigational agents (para 4-8).
- o The use of cancer cooperative group protocols (para 4-8).
- o The storage and accountability of investigational drugs and devices (para 4-10).
- o The use of approved drugs for unapproved indications (para 4-12).
- o Emergency procurement of drugs and vaccines from foreign suppliers (paras 4-13 and 4-14).

Effective 4 February 1991

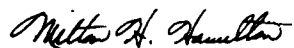
Medical Services

Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances

By Order of the Secretary of the Army:

CARL E. VUONO
General, United States Army
Chief of Staff

Official:



MILTON H. HAMILTON
Administrative Assistant to the
Secretary of the Army

History. This UPDATE printing publishes a revision of this publication. Because the publication has been extensively revised, the changed portions have not been highlighted.

Summary. This revision incorporates the provisions of the March 1987 rewrite of the Federal Regulations governing Investigational New Drug applications and Investigational Device Exemptions (published as title 21, parts 312 and 812, respectively, Code of Federal Regulations (21 CFR 312, 812)). This revision discusses Department of the Army-sponsored, non-Department of the Army-

sponsored, and investigator-sponsored categories for Investigational New Drug applications and Investigational Device Exemptions. It distinguishes between the process of Investigational New Drug and Investigational Device Exemption approval and the approval of research protocols under an Investigational New Drug or Investigational Device Exemption.

Applicability. This regulation applies to research, development, test, and evaluation programs and clinical investigation programs conducted by the Army.

Proponent and exception authority. Not used.

Army management control process. This regulation is subject to the requirements of AR 11-2. It contains internal control provisions but does not contain checklists for conducting internal control reviews. A checklist will be published at a later date.

Supplementation. Supplementation of this regulation and establishment of command and local forms are prohibited without the prior approval of HQDA (DASG-RDZ),

5109 Leesburg Pike, Falls Church, VA 22041-3258.

Interim changes. Interim changes to this regulation are not official unless they are authenticated by the Administrative Assistant to the Secretary of the Army. Users will destroy interim changes on their expiration dates unless sooner superseded or rescinded.

Suggested Improvements. The proponent agency of this regulation is the Office of The Surgeon General. Users are invited to send comments and suggested improvements on DA Form 2028 (Recommended Changes to Publications and Blank Forms) directly to the Assistant Surgeon General for Research and Development, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21702-5012.

Distribution. Distribution of this publication is made in accordance with the requirements on DA Form 12-09-E, block number 3421, intended for command level D for the Active Army and U.S. Army Reserve. This publication is not distributed to the Army National Guard.

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Chapter 1 Introduction

1-1. Purpose

This regulation prescribes Department of the Army (DA) policies and procedures applicable to the use of investigational drugs and devices and approved drugs for unapproved indications in humans and to the use of Schedule I controlled drug substances.

1-2. References

Required and related publications and referenced forms are listed in appendix A.

1-3. Explanation of abbreviations and terms

Abbreviations and special terms used in this regulation are explained in the glossary.

1-4. Overall principles and guidance

a. Research with investigational drugs and devices is of importance to the DA because

(1) The research, development, test, and evaluation (RDTE) of new drugs and devices designed to treat or prevent diseases that threaten the fighting strength of the soldier are of strategic importance.

(2) Clinical investigations of new drugs and devices within Army medical treatment facilities (MTFs) and dental treatment facilities (DTFs) foster the development of new treatment modalities for the benefit of all Defense Enrollment Eligibility Reporting System eligible beneficiaries. Such clinical investigations are also an integral part of graduate medical education programs conducted at Army medical centers.

b. Procedures to be followed to ensure protection of the rights and welfare of human subjects who participate in investigational drug or device research will be those described in AR 70-25, for RDTE organizations, or AR 40-38, for clinical investigation services, as appropriate. Procedures to be followed to ensure humane use of animals in drug and device research will be those described in AR 70-18/SECNAVINST 3900.38B/AFR 169-2/DARPAINST 18/DNAINST 3216.1B/USUHSINST 3203.

c. Acceptable methods of obtaining funding for clinical investigation of investigational drugs and devices through grants and gifts are described in AR 40-38.

d. Nothing in this regulation is intended to supersede health hazard or safety reviews required by other Army regulations.

e. The guidance in this regulation pertains to the following:

(1) Use of investigational drugs and devices in humans to include Schedule I controlled substances in Army MTF, DTF, and RDTE organizations.

(2) Nonclinical use (that is, animal use *or in vitro* testing) of Schedule I controlled substances.

(3) Use of approved drugs for unapproved indications in humans.

Chapter 2 Responsibilities

2-1. The Surgeon General (TSG)

TSG will—

a. Prepare policies and regulations for research using investigational drugs, devices, or Schedule I substances.

b. Establish and maintain the Human Use Review and Regulatory Affairs Office attached to the U.S. Army Medical Research and Development Command and reporting to the Assistant Surgeon General for Research and Development.

c. Be the approving authority for all research protocols involving the use of DA-sponsored investigational drugs or devices.

d. Be the approving authority for all human use research protocols involving the use of Schedule I controlled substances regardless

of the agency sponsoring the protocol or Investigational New Drug (IND) application.

2-2. Commander, U.S. Army Health Services Command (HSC)

The Commander, HSC, will—

a. Be the approving authority for all protocols involving non-DA-sponsored or investigator-sponsored investigational drugs or devices used within HSC except those involving Schedule I controlled substances.

b. Establish and maintain, within the U.S. Army Health Care Studies and Clinical Investigation Activity, the Clinical Investigation Program Division to coordinate and monitor clinical investigations that involve non-DA-sponsored and investigator-sponsored investigational drugs or devices.

c. Ensure that all requirements of this regulation, AR 70-25, and AR 40-38 are satisfied prior to the approval of clinical investigations involving non-DA-sponsored or investigator-sponsored investigational drugs or devices.

d. Be the approving authority for emergency procurement and use of investigational drugs in facilities that are organizationally a part of HSC.

2-3. Commanders, 7th Medical Command (7th MEDCOM) and 18th Medical Command (18th MEDCOM)

When a clinical investigation involving an investigational drug or device is proposed, the 7th and 18th MEDCOM Commanders will—

a. Be the approving authority for all protocols involving non-DA-sponsored or investigator-sponsored investigational drugs or devices used within their commands except those involving Schedule I controlled substances.

b. Ensure that all requirements of this regulation, AR 70-25, and AR 40-38 are satisfied prior to the approval of clinical investigations involving non-DA-sponsored or investigator-sponsored investigational drugs or devices.

c. Be the approving authority for emergency procurement and use of investigational drugs in facilities that are organizationally a part of their command.

2-4. Commander, U.S. Army Medical Department Activity—Japan (U.S. Army MEDDAC—Japan)

The Commander, U.S. Army MEDDAC—Japan, will—

a. Be the approving authority for emergency procurement and use of investigational drugs used at the U.S. Army MEDDAC—Japan.

b. Coordinate directly with the Human Use Review and Regulatory Affairs Office, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21702-5012, for review and approval of all protocols involving investigational drugs or devices.

2-5. Commanders of RDTE organizations

When research involving an investigational drug or device is proposed, commanders of RDTE organizations will ensure that all requirements of this regulation and AR 70-25 are satisfied.

2-6. Other responsible parties

a. The Chief, Human Use Review and Regulatory Affairs Office (HURRAO), will—

(2) Submit DA-sponsored IND applications and Investigational Device Exemptions (IDEs) directly to the Food and Drug Administration (FDA).

(2) Prepare and maintain records of all correspondence with the FDA concerning DA-sponsored IND applications and IDEs.

(3) Submit DA-sponsored New Drug Applications (NDAs) directly to the FDA.

(4) Conduct adverse drug reaction reporting and postmarketing surveillance programs for DA-sponsored, approved NDAs.

(5) Provide administrative support for the Human Subjects Research Review Board (HSRRB).

(6) Coordinate review and approval of all protocols involving investigational drugs or devices at U.S. Army MEDDAC—Japan.

b. HSRRB members will—

(1) Review and recommend to TSG the approval, deferral, or disapproval of research protocols involving investigational drugs or devices for which DA is the IND or IDE sponsor.

(2) Review and recommend to TSG the approval, deferral, or disapproval of research protocols involving investigational drugs or devices conducted under RDTE programs regardless of the individual or agency sponsoring the IND or IDE.

(3) Review and recommend to TSG the approval, deferral, or disapproval of all human use protocols involving the use of Schedule I controlled substances in Army conducted or sponsored research programs.

c. The sponsor of an IND or IDE will—

(1) Prepare and submit the IND or IDE to the FDA.

(2) Maintain records of all correspondence with the FDA concerning IND or IDE applications.

(3) Notify the FDA, all investigators, and approving human use committees of any significant adverse events, as defined in 21 CFR 312.32 resulting from the use of the investigational drug or device.

(4) Perform all other duties of the sponsor of an IND or IDE as detailed in 21 CFR 312 or 812.

d. The investigator will—

(1) Prepare a protocol in accordance with the policies and procedures of AR 40–38 for clinical investigations or AR 70–25 for RDTE funded research.

(2) Provide for protection of the rights and welfare of research volunteers in accordance with the policies and procedures of AR 40–38 for clinical investigations or AR 70–25 for RDTE funded research.

(3) Maintain adequate records of the receipt, storage, use, and disposition of all investigational drugs, devices, or Schedule I controlled substances.

(4) Prepare progress reports, including annual reports, required by the approving human use committee (HUC) or institutional review board (IRB), regulatory agencies, and the sponsor of the IND or IDE (see app B).

(5) Report serious and/or unexpected adverse experiences involving the use of an investigational device or drug to the sponsor and the HUC or IRB.

(6) Ensure that investigational drugs or devices are administered to subjects only under his or her personal supervision or the personal supervision of a previously approved associate investigator.

e. The investigator-sponsor will comply with paragraphs *c* and *d* above.

Chapter 3

Submission of Investigational new Drug Applications and Investigational Device Exemptions

3–1. General guidance

a. An approved IND or IDE is required in order to use investigational drugs or devices in clinical investigation or human research protocols. The approving authority for an IND or IDE is the FDA. The sponsor of the IND or IDE is responsible for filing the IND or IDE with the FDA and for all subsequent correspondence and recordkeeping associated with the IND or IDE. Records of IND or IDE maintained by DA agencies will be maintained in accordance with AR 25–400–2.

b. The format for an IND submission is outlined at appendix C. The format for an IDE submission is outlined at appendix D. A detailed description of IND requirements is published at 21 CFR 312. A detailed description of IDE requirements is published at 21 CFR 812.

c. The clinical investigation or research protocol that describes how an investigational drug or device is to be investigated is a

portion of the IND or IDE. Procedures for submission and approval of these protocols are addressed in chapter 4 of this regulation.

3–2. Department of Army-sponsored IND or IDE

a. Submission and management of a DA-sponsored IND or IDE is the responsibility of the Assistant Surgeon General for Research and Development.

b. A DA-sponsored IND or IDE is prepared for submission by the U.S. Army Medical Materiel Development Activity, Fort Detrick, Frederick, MD 21702–5009. The IND or IDE is then forwarded to the Human Use Review and Regulatory Affairs Office, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21702–5012. The HURRAO submits the IND or IDE to the appropriate office of the FDA and is responsible for preparing and maintaining records of all communications with the FDA concerning a DA-sponsored IND or IDE.

3–3. Non-DA-sponsored IND or IDE

For a non-DA-sponsored IND or IDE the sponsor is usually a commercial pharmaceutical or device manufacturer. The IND or IDE sponsor will submit the IND or IDE to the FDA and is responsible for all correspondence with the FDA concerning the IND or IDE.

3–4. Investigator-sponsored IND or IDE

a. An individual investigator may sponsor an IND or IDE. In this circumstance the investigator will apply directly to the FDA to obtain FDA approval to use the investigational drug or device. The investigator-sponsor will prepare and maintain records of all correspondence with the FDA.

b. If the investigator-sponsor is an active duty member or civilian employee of the U.S. Army in the HSC, an information copy of the IND or IDE submission and any subsequent correspondence with the FDA will be sent to Commander, U.S. Army Health Services Command, ATTN: HSHN–I, Fort Sam Houston, TX 78234–6000. Investigator-sponsors in 7th or 18th MEDCOM will send a copy of the IND or IDE submission, and any subsequent correspondence with the FDA, to their respective MEDCOM commander or designee. After appropriate review, these headquarters will forward copies to the Human Use Review and Regulatory Affairs Office, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21702–5012.

Chapter 4

Procedures for Use of Investigational Drugs and Devices in U.S. Army Medical Treatment Facilities, Dental Treatment Facilities, and Research Facilities

4–1. General guidance

Acceptance by the FDA of an IND or IDE submission does not constitute approval to conduct research or clinical investigations with investigational drugs or devices in Army facilities. Research or clinical investigation protocols that employ investigational drugs or devices will be prepared in accordance with AR 40–38 or AR 70–25. Approval to conduct the research or clinical investigation must be obtained as described below depending on the sponsorship of the IND or IDE and the funding source for the research or clinical investigation.

4–2. Approval of protocols conducted with a DA-sponsored investigational drug or device

a. For research funded under RDTE appropriated funds the protocol will be—

(1) Reviewed by the human use and scientific review committees of the facility conducting the research.

(2) Reviewed and approved by the commander of the facility where the research will be conducted.

(3) Forwarded to the Human Use Review and Regulatory Affairs Office, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21702–5012.

(4) Reviewed by TSG’s HSRRB prior to the start of research.

(5) Forwarded to TSG for action, as appropriate.

b. For clinical investigations funded by other than RDTE appropriated funds the protocol will be—

(1) Reviewed by the HUC and clinical investigation committee of the MTF or DTF where the investigation will be conducted. If the MTF or DTF at which the research is to be conducted does not have a clinical investigation committee and/or HUC, these reviews may be accomplished at the regional medical center with which the MTF or DTF is affiliated.

(2) Reviewed and approved by the commander of the MTF or DTF where the investigation will be conducted.

(3) Reviewed and approved by the HSC, 7th MEDCOM, or 18th MEDCOM commander, as appropriate.

(4) Forwarded to the Human Use Review and Regulatory Affairs Office, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21702–5012.

(5) Reviewed by TSG’s HSRRB prior to the start of the clinical investigation.

(6) Forwarded to TSG for action, as appropriate.

4–3. Approval of protocols conducted with a non-DA-sponsored investigational drug or device

a. If the research is funded under RDTE appropriated funds, the protocol will be reviewed and approved as described in paragraph 4–2a.

b. If the clinical investigation is funded by other than RDTE appropriated funds the protocol will be—

(1) Reviewed by the HUC and clinical investigation committee of the MTF or DTF where the research will be conducted. If the MTF or DTF at which the research is to be conducted does not have a clinical investigation committee and/or HUC, these reviews may be accomplished at the regional medical center with which the MTF or DTF is affiliated.

(2) Reviewed and approved by the commander of the MTF or DTF where the research will be conducted.

(3) Reviewed and approved by the HSC, 7th MEDCOM, or 18th MEDCOM commander, as appropriate, prior to the start of the clinical investigation.

4–4. Approval of protocols conducted with investigator-sponsored investigational drugs or devices

a. If the research is funded under RDTE appropriated funds the protocol will be reviewed and approved as described in paragraph 4–2a.

b. If the clinical investigation is funded under other than RDTE appropriated funds the protocol will be reviewed and approved as described in paragraph 4–3b.

4–5. Clinical use of Schedule I controlled substances

a. For approval to use a Schedule I drug in human subjects, a protocol will be submitted as described in paragraph 4–2. A statement of the security, audit, and control provisions for the Schedule I substance will accompany the protocol and IND submissions.

b. The sponsor of the IND will provide the investigator with the following statement:

I hereby certify that on *(date)*, pursuant to 21 USC 355(i) and 21 CFR 312.1, I, *(Name and address of IND sponsor)* submitted an Investigational New Drug (IND) application to the Food and Drug Administration for:

(Name of investigational drug).

(Date)

(Signature of applicant)

For a DA-sponsored IND the statement will be provided by the

HURRAO. The statement will be forwarded in triplicate by the investigator along with a Drug Enforcement Administration Certificate of Registration (DEA Form 225) to Drug Enforcement Administration, Department of Justice, P.O. Box 28083, Central Station, Washington, DC 20005.

4–6. Nonclinical use of Schedule I controlled substances

a. In order to conduct nonclinical research (that is, studies not involving human subjects) with Schedule I controlled substances, the researcher will submit DEA Form 225 along with three copies of the research protocol to Drug Enforcement Administration, Department of Justice, P.O. Box 28083, Central Station, Washington, DC 20005. The research protocol should provide the following information:

(1) Investigator’s name, address, and current DEA registration number, if any.

(2) Institutional affiliation of the researcher.

(3) Qualifications of the researcher, including curriculum vitae and an appropriate list of publications.

(4) Title of the research project.

(5) Statement of the purpose of the research.

(6) Name and amount of controlled substance(s) involved.

(7) Description of the research to include number of species of research animals, dosage to be administered, route and method of administration, and duration of the project.

(8) Location where the research will be conducted.

(9) Statement of security provisions for storing the controlled substance(s) in order to prevent diversion.

(10) Proof of institutional approval to conduct the research.

(11) Indication of an approved, funded grant, if any.

b. The researcher will also comply with the provisions of AR 70–18/SECNAVINST 3900.38B/AFR 169–2/DARPAINST 18/DNAINST 3216.1B/USUHSINST 3203.

4–7. Investigational use of radiopharmaceuticals

For approval to use an investigational radiopharmaceutical, the protocol must first be reviewed and approved by a radiation control committee. In addition, the review and approval process described in paragraphs 4–2, 4–3, or 4–4 will also be observed.

4–8. National Cancer Institute (NCI) cooperative group protocols and Group C cancer chemotherapy investigational agents

A physician requesting approval to conduct an investigation under an NCI cooperative group protocol or to use a Group C drug for treatment of individual patients will initiate the investigation or treatment in accordance with directives published by HSC, 7th MEDCOM, or 18th MEDCOM commander, as appropriate.

4–9. Medical emergencies

a. A physician seeking approval for one-time use of an investigational drug for a patient in an emergency situation must contact the agency or individual sponsoring the IND for the drug. If the sponsor agrees to release the drug for emergency use, it is the sponsor’s responsibility to obtain permission from the FDA to supply the drug to the requesting physician.

b. Before the drug may be used in an Army MTF the physician must, through his or her MTF commander, obtain the approval of the HSC, 7th MEDCOM, or 18th MEDCOM commander or designee. Within HSC, requests for emergency use of investigational drugs should be directed to the Commander, U.S. Army Health Care Studies and Clinical Investigation Activity, Fort Sam Houston, TX 78234–6060, AUTOVON 471–4541/2511. Commander of U.S. Army MEDDAC–Japan may approve emergency use of investigational drugs at that MEDDAC. Requests must include the patient’s name; diagnosis; name, quantity, and source of the drug; medical officer responsible for the patient; and nature of the emergency. In cases where approval is granted, the HSC, MEDCOM commander, or Commander, U.S. Army MEDDAC–Japan will forward this information to the Medical Consultant at The

Office of The Surgeon General, HQDA (SGPS-CP-M), 5109 Leesburg Pike, Falls Church, VA 22041-3258, AUTOVON 289-0148; and the Human Use Review and Regulatory Affairs Office, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21702-5012.

c. It is the responsibility of the treating physician to notify appropriate clinical investigation committee and HUCs of the use of the investigational drug.

d. In cases where emergency use is approved, the treating physician will send a report summarizing the case to The Assistant Surgeon General for Research and Development, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21702-5012, and to HSC, 7th MEDCOM, or 18th MEDCOM commander, as appropriate. For HSC facilities the report will be sent to U.S. Army Health Care Studies and Clinical Investigation Activity, ATTN: HSHN-I, Fort Sam Houston, TX 78234-6060. In addition to describing the circumstances and outcome of the use of the investigational drug the physician will include copies of any forms or reports furnished to a commercial manufacturer, other non-DA agency, or an individual in connection therewith.

4-10. Investigational drug and device use control

a. *Procurement and storage.* Investigational drugs and devices are the property of the sponsor throughout the study. The pharmacy is the appropriate storage area for all investigational drugs in MTFs. The pharmacy is responsible for the proper recording, labeling, storage, and dispensing of investigational drugs in accordance with the investigator's written orders. The dispensing of investigational drugs should be integrated with the rest of the inpatient or outpatient drug distribution system with respect to packaging, labeling, order receiving, profile maintenance, and delivery. The storage of these drugs, however, should be separate from the regularly stocked drugs in the pharmacy. An exception to the above storage procedure would be radiopharmaceutical dosage forms, which should be stored in the nuclear medicine service's area if appropriate security is provided. The preferred area for storing radiopharmaceuticals is a nuclear pharmacy co-located with the nuclear medicine service. The nuclear medicine service would be responsible for proper recordkeeping, labeling, storage, and handling of the radiopharmaceuticals subject to appropriate regulations. Otherwise, a complete record of each investigational drug will be maintained by the pharmacy and will contain the following information:

- (1) Name of drug, dosage form, and strength.
- (2) Title of protocol under which drug is used.
- (3) Name(s) of investigator(s).
- (4) Manufacturer or other source of drug.
- (5) Amount of drug and date received.
- (6) Perpetual inventory record of on-hand stocks of drug.
- (7) Expiration date.
- (8) Lot or control number.
- (9) Name(s) of subject(s) using drug.
- (10) Date(s) on which subject(s) receive drug and quantity dispensed.

Investigational device storage, security, and recordkeeping is determined based on the nature and use of the device. A knowledgeable user of the device will act as custodian of the device. The chief, clinical support division will maintain a listing of investigational devices in use in the hospital and the custodians for each device. The commander or director of research facilities (such as laboratories) that do not have a pharmacy will appoint a specific and knowledgeable custodian to maintain accountability for all investigational drugs or devices as noted above. If the research facility is located near an MTF with a pharmacy, it is recommended that the research facility commander or director pursue a cooperative agreement with the MTF commander to use the MTF pharmacy as custodian of investigational drugs. Security requirements for investigational drugs will be the same as those recognized for security of prescription drugs or drugs under DEA control, if applicable. Discrepancies in inventory record balances and on-hand balances will be resolved by

the custodian of the investigational drug record. Discrepancies unable to be resolved by the custodian will be reported to the principal investigator and, if necessary, to the sponsor and FDA.

b. *Dispensing.* The pharmacy service or other designated investigational drug custodian will dispense investigational drugs on DD Form 1289 (DOD Prescription) or DA Form 4256 (Doctor's Orders) signed by the principal investigator or a co-investigator. In addition to labeling requirements specified in AR 40-2 for dispensed medications, the label of an investigational drug will indicate the investigational nature of the drug (that is, "For Investigational Use only," or "Investigational Drug").

c. *Administration.* Nurses and other healthcare professionals called upon to administer investigational drugs will be provided the necessary information about basic pharmacology, storage, adverse effects, precautions, authorized prescribers, patient monitoring guidelines, and overall study objectives and procedures. For investigational devices, users will be trained in the use of the device and must have adequate knowledge of necessary calibration, application, and general use procedures for the device.

d. *Records.* Records for DA-sponsored investigational drugs and devices will be maintained as follows: For Phases I, II, and III, the investigator will ensure that, in addition to clinical records, a separate record is maintained. The record will include, as a minimum: A copy of the protocol and consent form (to include a Privacy Act Statement as prescribed by AR 340-21) used in the study; a list of subjects receiving the drug or device; the name, lot number, date and quantity of the drug or device; and, as appropriate, tests and laboratory procedures. For non-DA-sponsored investigational drugs or devices the investigator will also comply with any recordkeeping requirements imposed by the sponsor of the investigation.

e. *Drug information.* The commander of the facility in which the research is being conducted will establish a central unit where basic essential information on investigational drugs is maintained and can be made available to all authorized personnel. In MTFs, the pharmacy is the appropriate location for such a drug information center and the pharmacy and therapeutics committee (P and T committee), or therapeutic agents board (TAB), should act as the monitor of such activities. At a minimum, information on dosage, indications, expected effects, potential untoward effects, contraindications, storage requirements, preparation and administration instructions, and names and telephone numbers of principal and authorized associate investigators should be made available to personnel called upon to administer investigational drugs. Arrangements must be made to have required information available 24 hours a day.

f. *Device information.* The custodian of an investigational device will establish an information file for the device. This file will, as appropriate, contain the kind and quality of information described in paragraph e above for drugs.

g. *Retention period.* All records required by this paragraph will be kept for a minimum of 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, for a minimum of 2 years after the investigation is discontinued and FDA is notified. See also AR 25-400-2 (file no. 40-38a or 70-25a) for additional recordkeeping requirements.

4-11. Reporting of adverse experiences with investigational drugs or devices

a. An investigator who observes a serious and unexpected adverse reaction to an investigational drug or device will immediately notify the sponsor of the IND or IDE. For a DA-sponsored IND or IDE this notification will be made to the Human Use Review and Regulatory Affairs Office, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD HR, Fort Detrick, Frederick, MD 21702-5012 (AUTOVON 343-2165, Commercial (301) 663-2165). The investigator will also notify all HUCs that reviewed and approved the research protocol. Such reports must be rendered within 10 working days of the event.

b. Serious adverse experiences include any that are fatal, life

threatening, permanently disabling, require inpatient hospitalization, or result in congenital anomalies, cancer, or overdose.

c. An unexpected adverse experience is any adverse experience not identified in nature, severity, or frequency in the investigator brochure supplied by the sponsor of the IND.

4-12. Use of an approved drug for an unapproved indication

Any marketed drug is an investigational new drug if a labeling change made after 9 October 1962 recommends or suggests new conditions of use under which the drug is not generally recognized as safe and effective by qualified experts. The preceding stipulation is not intended to limit the therapeutic options that a physician may exercise in the course of practice when treating individual patients. However, in situations where data on drug effects from one or more patients are being systematically recorded by a physician for the purpose of substantiating or refuting a claim of therapeutic efficacy in an unlabelled indication for an approved drug, the physician is conducting a clinical investigation, and must adhere to the requirements of AR 40-38 (for clinical investigations) or AR 70-25 (for RDTE funded research) in conducting the investigation. Such a clinical investigation of a drug product that is lawfully marketed in the United States must be done under an IND, unless *ALL* of the following apply:

a. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used for any other significant change in the labeling for the drug.

b. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the investigation is not intended to support any other significant change in the advertising for the product.

c. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

d. The investigation is conducted in compliance with the requirements for human use review and informed consent set forth in AR 40-38.

e. The drug is not represented in a promotional context as being safe or effective for the purposes for which it is being investigated.

4-13. Emergency procurement of drugs from foreign suppliers

a. It is the policy of TSG that drugs used in an Army MTF will be those approved by the FDA and procured from suppliers in the United States. However, it is recognized that situations may arise when a drug cannot be procured in a timely manner from a supplier in the United States, especially in an MTF located outside of the continental United States. If an FDA approved drug is unavailable from a U.S. supplier, drugs distributed by foreign suppliers may be procured, provided one of the following circumstances exists:

(1) The drug is needed to save life, limb, or eyesight and the time required to procure the drug from a U.S. supplier would endanger the patient's well being.

(2) The drug is needed to continue life sustaining chronic therapy and the time required to procure the drug from a U.S. supplier would cause an interruption of such therapy as to endanger the patient's well being.

b. Drugs purchased from foreign suppliers must contain the same active ingredient(s) and be formulated in the same dosage form as the like product procured from a U.S. supplier. If the active ingredient or dosage form of a product procured from a foreign supplier is not available in the United States, the drug will be considered investigational and the procedures described above for use of an investigational drug apply.

c. The procedures for emergency procurement of drugs from foreign suppliers are as follows:

(1) The chief of pharmacy services will initiate the request for

purchase of a drug from a foreign supplier when in his or her professional judgment such a purchase is necessary.

(2) All purchase requests for drugs from a foreign supplier will be signed by the MTF commander or his or her designee.

(3) The chief of pharmacy services will maintain a record of the use of drugs procured from a foreign supplier. A copy of this record will be forwarded to the HSC, 7th MEDCOM, or 18th MEDCOM commander, as appropriate, or designee within 5 working days after the drug procured from the foreign supplier is no longer in use. A copy of the record will also be presented to the P and T committee or TAB at the MTF at the next regularly scheduled meeting. This record will consist of—

(a) The trade name, generic name, manufacturer, lot number, expiration date, amount, and source of the drug.

(b) A brief justification of why procurement of the drug from a foreign supplier was necessary.

(c) The name(s) and social security number(s) of patient(s) who received the drug procured from a foreign supplier.

4-14. Emergency procurement of vaccines and biological products from foreign suppliers

Vaccines and other biological products may not be procured from foreign suppliers if the same vaccine or biological product is available from a U.S. supplier. If there is a need to procure a vaccine or biological product that is not available from a supplier in the United States, the vaccine or biological product will be considered investigational and the procedures described above for use of an investigational drug apply.

Appendix A References

Section I Required Publications

AR 25-400-2

The Modern Army Recordkeeping System (MARKS). (Cited in paras 3-1a and 4-10g.)

AR 40-2

Army Medical Treatment Facilities General Administration. (Cited in para 4-10b.)

AR 40-38

Clinical Investigation Program. (Cited in paras 1-4b and c, 2-2c, 2-3b, 2-6d(1) and (2), 4-1, and 4-12 and in the glossary.)

AR 70-18/SECNAVINST 3900.38B/AFR 169-2/DARPAINST 18/DNAINST 3216.1B/USUHSINST 3203

The Use of Animals in DOD Programs. (Cited in paras 1-4b and 4-6b)

AR 70-25

Use of Volunteers as Subjects of Research. (Cited in paras 1-4b, 2-2c, 2-3b, 2-5, 2-6d(1) and (2), 4-1, and 4-12.)

AR 340-21

The Army Privacy Program. (Cited in para 4-10d.)

DOD Directive 3216.2

Protection of Human Subjects in DOD-Supported Research. (Cited in the glossary.)

21 CFR 312

Investigational New Drug Application. (Cited in the summary paragraph and paras 2-6c(3) and (4), 3-1b, and 4-5b.)

21 CFR 812

Investigational Device Exemptions. (Cited in the summary paragraph and paras 2-6c(4) and 3-1b.)

21 USC 355

Federal Food, Drug, and Cosmetic Act. (Cited in para 4-5b.)

Section II Related Publications

TB MED 525

Control of Hazards to Health from Ionizing Radiation Used by the Army Medical Department

21 CFR 314

Applications for FDA Approval to Market a New Drug or Antibiotic Drug

21 CFR 361.1

Radioactive Drugs for Certain Research Uses

21 CFR 1301

Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances

21 CFR 1308.11

Schedules of Controlled Substances, Schedule I

45 CFR 46

Institutional Review Boards

Section III Prescribed Forms

DA Form 4256

Doctor's Orders

DD Form 1289

DOD Prescription

DEA Form 225

Drug Enforcement Administration Certificate of Registration. (This form may be obtained from Registration Unit, Drug Enforcement Administration, Department of Justice, Post Office Box 28083, Central Station, Washington, DC 20005.)

FDA Form 1571

Investigational New Drug Application (IND) Cover Sheet. (This form may be obtained from Reports Clearance Officer, PHS, Hubert H. Humphrey Building, Room 721-H, 200 Independence Ave., S.W., Washington, DC 20201, ATTN: PRA.)

Section IV Referenced Forms

This section contains no entries.

Appendix B Progress Reports for Investigational Drugs and Devices

B-1. Reports

The investigator will provide the sponsor of the IND or IDE with a periodic report (at least annually) of the progress of investigations conducted under the IND or IDE. It is the responsibility of the sponsor to consolidate these reports and forward the information to the FDA. For a DA-sponsored IND or IDE, the information will be submitted to Commander, U.S. Army Medical Materiel Development Activity, Fort Detrick, Frederick, MD 21702-5012.

B-2. Progress reports for investigational drugs

Periodic reports on an investigational drug will address the following:

a. A brief summary of the status of the study in progress and each study completed during the previous year to include the—

(1) Title of the study, its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) Total number of subjects initially planned for inclusion in the study, number entered to date, number whose participation was completed as planned, number who withdrew from participation and the reason for their withdrawal.

b. A summary of information obtained during the previous year's investigation to include a—

(1) Narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) Summary of all IND safety reports submitted during the previous year.

(3) List of subjects who died during participation in the investigation and cause of death for each.

(4) List of subjects who dropped out of the investigation in association with any adverse experience regardless of whether or not the adverse experience is thought to be drug related.

(5) Brief description of what information, if any, was obtained pertinent to an understanding of the drug's actions, including, for example, dose response and bioavailability information.

(6) List of preclinical studies completed or in progress during the past year and a summary of the major preclinical findings.

(7) Summary of any significant manufacturing or microbiological changes made during the past year.

c. A description of the general investigational plan for the coming year.

d. A description of any revisions in the investigator brochure and a copy of the new brochure.

e. A description of any significant Phase I protocol modifications made during the previous year, not previously reported as a protocol amendment to the IND.

f. A brief summary of significant foreign marketing developments.

g. If desired, a log of any outstanding business with respect to the IND requiring a response from the FDA.

B-3. Progress reports for investigational devices

For investigational devices the investigator will submit progress reports on the investigation to the sponsor, the monitor, and the reviewing HUC at regular intervals, but in no event less often than yearly. The investigator will also report—

a. Any unanticipated adverse device effect occurring during an investigation. These reports are made to the sponsor and the reviewing HUC as soon as possible, but not later than 10 working days after the investigator learns of the event.

b. Withdrawal of approval by the reviewing HUC to the sponsor within 5 working days.

c. Any deviations from the investigational plan to the sponsor and the reviewing HUC. If the deviation is to protect the life or physical well being of a subject, the investigator will notify the reviewing HUC and the sponsor as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such emergency, prior approval from the sponsor is required for changes in or deviations from a plan and, if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, approval from the FDA and the reviewing HUC is also required.

d. The use by the investigator of a device without obtaining informed consent. The investigator will report such use to the sponsor and the reviewing HUC within 5 working days after the use occurs.

e. To the sponsor and the reviewing HUC within 3 months after the termination or completion of an investigation. This report is a final report by the investigator.

f. Upon request by a reviewing HUC or the FDA, accurate, complete, and current information about any aspect of the investigation.

Appendix C Investigational New Drug Application Format

C-1. Front matter

Include identifying information, a cover sheet (FDA Form 1571 (Investigational New Drug Application (IND) Cover Sheet)), and a table of contents.

C-2. Introductory statement and general investigation plan

a. Introductory statement giving—

- (1) The name of the drug.
- (2) All active ingredients.
- (3) The pharmacological class of the drug.
- (4) The structural formula of drug (if known).
- (5) The formulation of the dosage form to be used.
- (6) The route of administration to be used.
- (7) The broad objectives and planned duration of the proposed clinical investigation.

b. A brief summary of previous human experience with the drug that may be relevant to the safety of the proposed clinical investigations.

c. The identification of any countries where the drug may have been removed from use for any reason relating to safety and effectiveness and the reasons for removal from use.

d. A brief description of the overall plan for investigating the drug product for the following year to include—

- (1) The rationale for the study.
- (2) Indications to be studied.

(3) The general approach to be followed in studying the drug.

(4) The kinds of clinical trials to be conducted.

(5) The estimated number of patients to be given the drug.

(6) Any particularly severe risks to human subjects that are anticipated.

C-3. Investigator brochure

Provide a copy of the investigator brochure prepared by the IND sponsor.

C-4. Protocol for each planned study

The protocol includes—

- a. A statement of the objective and purpose of the study.
- b. The name, address, and qualifications of each investigator.
- c. The name and address of the research facility and each reviewing HUC or institutional review board.
- d. Inclusion and exclusion criteria for the study and an estimate of the number of patients to be studied.
- e. A description of the design and methods of the study.
- f. The method for determining doses to be given, planned maximum dose, and duration of patient exposure to the drug.
- g. A description of observations and measurements to be made.
- h. A description of procedures and laboratory tests to be used to monitor drug effects and minimize risks.

C-5. Product formulation information

Provide chemistry, manufacturing, and control information for drugs and placebos used.

C-6. Adequate information about pharmacological and toxicological studies

These are studies of the drug involving laboratory animals or *in vitro* studies that have led the sponsor to conclude that the drug is safe to test in humans. This information should include—

- a. Pharmacological effects.
- b. Absorption, metabolism, distribution, and excretion data.
- c. The mechanism of action.
- d. Results of acute, subacute, and chronic toxicity tests in animals.

C-7. Previous human experience with the drug

This information may come from previous investigations in the United States or elsewhere or use of the drug in a foreign country.

C-8. Summary of additional information (if appropriate)

This information is to aid in the evaluation of the IND such as drug dependence, abuse potential, and radiation absorbed dose.

C-9. Requested relevant information

If requested by the FDA, the applicant must also include any other relevant information needed for review of the application.

Appendix D Investigational Device Exemption Application Format

C-6. Sponsor information

Include the name and address of the sponsor.

D-2. History

Include a complete report of prior investigations of the device.

D-3. Investigational plan

If no HUC has reviewed the investigational plan, a complete plan must be submitted to the FDA. If a HUC has reviewed the investigational plan, a summary of the plan may be submitted. The investigational plan will include—

- a. The name and intended use of the device and the objectives and duration of the investigation.
- b. A written protocol describing the methodology to be used and

an analysis of the protocol demonstrating that the investigation is scientifically sound.

c. A description and analysis of all increased risks to which subjects will be exposed by the investigation, methods by which risks will be minimized, a justification for the investigation, and a description of the patient population to include number of subjects, age, sex, and condition.

d. A description of each important component, ingredient, property, and principle of operation of the device and of each anticipated change in the device during the course of the investigation.

e. A description of the procedures to be used to monitor the investigation and the name and address of any monitor.

f. Copies of all labeling for the device.

g. Copies of all consent forms and information materials to be given to subjects or users of the apparatus.

h. A list of names, locations, and chairpersons of all HUCs that have been or will be asked to review the investigation and certification of action taken by reviewing committees.

i. The name and address of each institution at which a part of the investigation may be conducted.

j. A description of records and reports that will be maintained on the investigation in addition to those required by the FDA.

D-4. Agreements and investigators list

An example of the agreements to be entered into by all investigators of the device to comply with investigator's obligations and a list of names and addresses of all investigators who have signed such agreements.

D-5. Certification

A certification that the list of investigators includes all the investigators participating in the investigation and that no investigator will be added until he or she has signed the investigator's agreement.

D-6. Selling a device

If the device is to be sold, the selling price must be stated along with an explanation as to why the sale does not constitute commercialization.

D-7. Environmental analysis report

If requested by the FDA, an environmental analysis report must be provided.

D-8. Other information

Any other relevant information that the FDA requests.

Glossary

Section I Abbreviations

CFR

Code of Federal Regulations

DA

Department of the Army

DEA

Drug Enforcement Administration

DOD

Department of Defense

DTF

dental treatment facility

FDA

Food and Drug Administration

HSC

U.S. Army Health Services Command

HSRRB

Human Subjects Research Review Board

HUC

human use committee

HURRAO

Human Use Review and Regulatory Affairs Office

IDE

Investigational Device Exemption

IND

Investigational New Drug (application)

IRB

institutional review board

MEDCOM

medical command

MEDDAC

(U.S. Army) Medical Department activity

MTF

medical treatment facility

NCI

National Cancer Institute

NDA

New Drug Application

P and T committee

pharmacy and therapeutics committee

RDTE

research, development, test, and evaluation

TAB

therapeutic agents board

TSG

The Surgeon General

Section II Terms

Adverse experiences

a. Serious. Any that are fatal, life threatening, permanently disabling, require in-patient hospitalization, or result in congenital anomalies, cancer, or overdose.

b. Unexpected. Any adverse experience not identified in nature, severity, or frequency in the investigator brochure supplied by the sponsor of the IND.

Approving authority

A military or civilian member of an organizational element of a DA component who has been delegated authority to approve the use of human subjects in research.

Associate investigator

A person who may be involved in the execution of research but does not have overall primary responsibility. The FDA refers to such an individual as a subinvestigator.

Clinical investigation

An organized inquiry into health problems for all conditions that are of concern in providing healthcare to beneficiaries of the military healthcare system, including active duty personnel, dependents, and retired personnel. The clinical investigation program is described in AR 40–38.

Co-investigator

A person who may be involved in the execution of research but does not have overall primary responsibility. The FDA refers to such an individual as a subinvestigator.

DA-sponsored IND

An IND application that identifies TSG or his or her designee as sponsor of the application.

Group C cancer chemotherapy investigational agents

Drugs that demonstrate efficacy within a tumor type in more than one study, alter the pattern of care of the disease in question, and are safely administered by properly trained physicians without requiring special supportive care facilities. The classification of an investigational drug into Group C and its distribution is administered by the NCI.

Human subject

a. A living individual about whom an investigator conducting research obtained data through interaction with the individual, including both physical procedures and manipulations of the subject or the subject's environment. The term does not include military or civilian personnel who are qualified to test by assignment to duties that call specifically for such qualifications, such as test pilots and test engineers.

b. A minor (child) is a person who has not

attained the legal age for consent to treatments or procedures involved in research under the applicable laws of the jurisdiction in which the research will be conducted.

c. Human subjects may be thought of as direct objects when the research is to determine the effects of a new system on humans (for example, the effects of a weapon's blast on hearing) or as indirect objects when a test is conducted to determine how humans affect the ultimate performance of a system (doctrine concepts; training programs).

Human Subjects Research Review Board

The principal body of the Office of The Surgeon General for review of clinical investigation and research activities utilizing human subjects.

Human use committee

A committee or board established to provide initial and continuing review of research involving the use of human subjects. A HUC is fundamentally similar to an IRB (42 CFR 46) but has somewhat different authority as compared to an IRB. Within DOD, authority to approve the use of human subjects in research is vested in commanders. Commanders act on the recommendation of validly constituted HUCs. Outside DOD, IRBs tend to be vested with this authority.

Investigational device

a. A device that is not generally used in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and is not generally recognized as safe and effective.

b. Research is usually, but not necessarily, initiated to determine if the device is safe or effective.

Investigational drug

A drug may be considered investigational when the composition is such that its proposed use is not recognized for the use under the conditions prescribed, or its proposed use is not recommended or suggested in its approved labeling. Experts qualified by scientific training and experience evaluate the safety and effectiveness of drugs to make this determination.

Investigator

An individual who actually conducts a clinical investigation; that is, under whose immediate direction the test article is administered or dispensed to a subject.

Investigator-sponsored IND

An IND application for which the principal investigator of the drug is also identified as the sponsor of the application.

NCI cooperative group

A cooperative group of investigators in the field of cancer therapy who are registered with and sponsored by the NCI, National Institutes of Health, Bethesda, Maryland, which provides financial support to the group.

Non-DA-sponsored IND

An IND application sponsored by an agency or an individual not affiliated with the DA.

Phases of an investigation for investigational drugs

a. Phase I starts after adequate animal and *in vitro* data have been obtained and covers the first administration to humans of an investigational drug or device. It includes, as appropriate, studies to determine human safety, metabolism, immunogenicity, absorption, elimination, and other pharmacological action, preferred route of administration, and dosage. Phase I studies generally include 20 to 80 subjects.

b. Phase II covers use of an investigational drug or device in a limited number of patients for specific disease control or prophylaxis. The purpose of phase II is to determine potential usefulness, determine dosage range, and gather additional pharmacologic and pharmacokinetic data, and collect additional toxicity data. Phase II studies generally include no more than several hundred subjects.

c. Phase III provides for assessment of the safety, effectiveness, and optimum dosage schedules of the investigational drug or device in a larger sample of patients. Phase III studies generally include several hundred to several thousand subjects and are designed to compare investigational therapy to standard therapy in controlled clinical trials.

Postmarketing surveillance

Postmarketing surveillance is performed on FDA approved drugs. Postmarketing surveillance is designed to determine patterns of drug utilization and gather additional efficacy, adverse reaction, and toxicity data under general marketing conditions. For approved NDA for which TSG of the Army is the sponsor, the conduct of postmarketing surveillance will be the responsibility of the HURRAO.

Protocol

The written, detailed plan by which research is to be conducted. The plan contains, as a minimum—

- a. The objectives of the project.
- b. The information to be collected.
- c. The means by which information will be collected and evaluated.
- d. An assessment of potential risk and benefits to subjects.
- e. Safety measures and other means to be used to reduce any risk to subjects.

Radiation control committee

A committee appointed by the commander to ensure that individual users of radioactive materials within the medical facility and each radionuclide used will be approved and controlled. The approval and control must be in accordance with the requirements specified in the conditions of the Nuclear Regulatory Commission license, the DA radioactive material authorization, and appropriate Federal directives.

Research

A systematic investigation that is designed to develop or contribute to generalizable knowledge. The term does not include individual or group training of military personnel such as combat readiness, effectiveness, proficiency, or fitness exercises (DOD Directive 3216.2.)

Research, development, test, and evaluation

The categories of research and development included in Program 6, Research and Development, and operational systems development contained in the Five-Year Defense Program.

Schedule I controlled drug substance

Any drug or substance by whatever official name, common or usual name, chemical name, or brand name listed in 21 CFR 1308.11; for example, heroin.

Sponsor

A person who initiates a clinical investigation but does not actually conduct the investigation; that is, the test article is administered to or dispensed to or used by a subject under the immediate direction of another individual. When an entity other than an individual (for example, a corporation or agency) initiates and conducts clinical investigation using one or more of its own employees, the corporation or agency is considered to be the sponsor and the employees are considered to be investigators.

Supplier (of a drug, vaccine, or biological product)

An activity that serves as a provider of drugs, vaccines, and biologicals used in an Army MTF. These providers include commercial pharmaceutical distributors, as well as elements of the military medical logistics system, such as installation medical supply accounts, U. S. Army medical materiel centers, Defense Personnel Support Center, and medical depots.

Treatment IND

An IND in which one of the protocols under the IND is a treatment protocol allowing the use of a promising investigational drug in patient care by physicians who agree to follow the protocol. Designation of treatment IND or treatment protocol status is made by the FDA.

Section III**Special Abbreviations and Terms**

This section contains no entries.

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